Fasting causes a 2 fold induction of PPARα in wild type mice (Fig. 4D), consistent with reports that this transcription factor mediates glucocorticoid-induced fatty acid oxidation during fast (20, 21). However, whilst 11βHSD-1$^{-/-}$ liver PPARα levels are higher than wild type levels during *ad lib* fed conditions, fasting induction of PPARα mRNA is abolished in 11βHSD-1$^{-/-}$ animals (Fig 4D). Despite the abolished induction of PPARα, the downstream target genes ACO and UCP-2 showed a fasting induction. This induction is smaller relative to the wild type ad lib to fasting induction. Such a modest induction could reflect the presence of relatively elevated ad lib fed PPARα levels in mice being activated by the increased levels of endogenous PPARα activators, fatty acids, during fasting. The glucocorticoid-inducible transcript apoAI also shows an attenuated rise on fasting, compatible with reduced effective glucocorticoid levels in hepatocytes (Fig 5B). In agreement with an attenuated fasting response, a blunted fast-mediated repression of the lipid esterification enzyme GPAT is observed in null mice compared to wild type mice (Fig. 3B). Also, fasting induction of CPT-I (Fig. 4A) appears normal and fasting plasma glucose is not significantly different between genotypes. This implies that the attenuation of glucocorticoid effects on fatty acid oxidation and gluconeogenesis is not dramatic enough to cause hypoglycaemia after a 24 hour fast in the 11βHSD-1$^{-/-}$ mice.

11βHSD-1 does not respond acutely to fasting/re-feeding in wild-type mice - To determine that the difference between wild type and 11βHSD-1$^{-/-}$ mice are not merely due to feeding-related alterations in 11βHSD-1 activity, transcript levels and activity of the wild type 11βHSD-1 is measured across the experimental groups. Neither 11βHSD-1 mRNA or activity levels are affected by a 24 hour acute fast or subsequent re-feeding (Fig. 7A, 7B). Thus, whilst the enzyme is critical for regulating the active intracellular glucocorticoid level, it does not appear to be acutely regulated by either the increased corticosterone (wild type, ad lib fed 25.2±7.2 versus wild type fasting 222 ±76 nmol/L, $p < 0.05$). Further, 11βHSD-1 mRNA and activity is not affected by the reduced insulin levels associated with fasting (wild type, ad lib 3131±81 versus wild type fasting 564±36 ng/ml) or with the subsequent influx of insulin upon re-feeding (4 hour re-fed value 6052±654 ng/ml).